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**VERFAHREN ZUR HERSTELLUNG VON OPTISCH AKTIVEM 2-SUBSTITUIERTEM
TETRAHYDROPYRAN-4-ON**

**PREPARATION DE TETRAHYDROPYRANE-4-ONES A SUBSTITUTION EN POSITION 2 ACTIVES
SUR LE PLAN OPTIQUE**

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WO-A-93/06235 **WO-A-93/06236**
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Description

[0001] THIS INVENTION relates to a Process for the Production of Optically Active 2-Substituted tetrahydropyran-4-ones.

[0002] Certain tetrahydropyran-4-ones are of interest as chemical intermediates in the production of biologically active materials, for example those of European Patents 465,812; 462,813; 409,413; 420,511; 410,661; 385,662 and 375,404. In at least some cases compounds of enhanced activity are produced if the tetrahydropyran-4-one is 2-substituted and is in the (S) configuration. Compounds of the (R) configuration are of possible research interest. WO 93/06235 and WO 93/06236 disclose the enzymatic resolution of trans-2-substituted-4-hydroxytetrahydropyran-2-ones and esters thereof.

[0003] This invention comprises a process of producing an optically active cis-2-substituted tetrahydropyran-4-ol or ester thereof which comprises stereospecifically esterifying a cis-2-substituted tetrahydropyran-4-ol using a stereospecific esterase or stereospecifically hydrolysing an ester thereof with a stereospecific hydrolase.

[0004] We have found that the invention may be carried out with surprisingly high stereo specificity.

[0005] If desired the hydrolysis of the ester product may be carried out using a stereospecific hydrolase in order to increase the optical purity further.

[0006] The cis 2-substituted tetrahydropyran-4-ols or esters react more readily in the invention than the trans compounds and the (R) compounds can be reacted stereospecifically both in esterification and hydrolysis thereby leaving the (S) compounds unconverted.

[0007] The racemic mixture of the 2-substituted tetrahydropyran-4-ol in substantially the cis form may be produced by reacting but-3-ene-1 ol with an aldehyde of formula X CHO in which X is the desired 2-substituent of the pyranol in the presence of an acid which is preferably sulphuric acid. X is suitably an alkyl for example, an ethyl or methyl group or a substituted alkyl for example mono or di fluoro-substituted alkyl for example methyl or ethyl group. A method for this process using H₂SO₄ as catalyst is described by Hanschke (Chem Ber (1955) vol 88 p 1053). Cis and trans orientations are lost on oxidation to the corresponding ketone but we have found the cis product to be very suitable for this invention.

[0008] The invention also comprises a process of producing an optically active cis-2-substituted tetrahydropyran-4-ol or ester thereof which comprises producing a cis-racemic 2-substituted tetrahydropyran-4-ol by reacting but-3-ene-1-ol with an aldehyde of formula XCHO in which X is the desired 2-substituent of the pyranol in the presence of an acid, esterifying the racemic mixture using a stereospecific esterase or esterifying the racemic mixture optionally non stereospecifically and hydrolysing it with a stereospecific hydrolase.

[0009] The esters may be made by normal methods, preferably using the free acids, acyl halides and/or anhydrides, in non stereospecific esterification. In stereospecific esterification it is preferred to transesterify with another ester, which is suitably a vinyl ester, as the by-product, acetaldehyde, is not involved in a back-reaction. It is preferred that the stereospecific esterification reaction and/or hydrolysis be carried out at a pH of 5 to 10, at least if excess water for example water of reaction, is present, more preferably 6 to 9, and a temperature of preferably 20 to 65°C, more preferably 25 to 50°C. The esters are preferably esters of lower alkanic acids having 2 to 8 carbon atoms, benzoic acid or substituted derivatives thereof. Preferably, the esters are separated from the alcohols.

[0010] The enzymes may be provided as such or as whole cells comprising them. It is preferred that they be immobilised so as to facilitate their separation from the product and, if desired, re-use.

[0011] The stereospecific esterification and/or hydrolysis step(s) may be carried out by mixing the reactant(s) with the enzyme, normally in the presence of at least an amount of water sufficient to allow enzyme activity and, in the case of hydrolysis to supply the water of reaction and optionally an inert solvent.

[0012] Preferred enzymes include those from *Humicola lanuginosa* for example that sold under the Trade Mark Lipolase and *Pseudomonas* for example that sold under the Trade Mark SAM II and more preferably those from *Candida antarctica*, for example that sold under the Trade Mark NOVOZYM.

[0013] Oxidation of the alcohol to the ketone is suitably carried out with a strong oxidising agent, for example chromic acid suitably in the presence of a strong acid for example sulphuric acid and an inert organic solvent for example a ketone. The temperature is preferably in the range 0 to 40°C for example 0 to 30°C.

[0014] If desired, the alcohol may be further reacted, for example by oxidation of the corresponding ketone in the presence of the ester. Any separation of the ester which is required may be carried out after such further reaction. The invention may be used as a route to either the product of the stereospecific reaction or to the unconverted isomer.

EXAMPLE 1

Preparation of Racemic Cis-2-Methyltetrahydro-(4H)-Pyran-4-ol Butyrate Ester

[0015] Racemic cis-2-methyltetrahydro-(4H)-pyran-4-ol was prepared by the method of E Hanschke (Chemische

Berichte (1955), volume 88, p 1053).

[0016] Typically esterification was carried out as follows.

[0017] A solution of cis-2-methyltetrahydro-(4H)-pyran-4-ol (20g, 0.172 mole) and triethylamine (20.2g, 0.20 mole) in dichloromethane (120ml) was cooled in an ice bath. Butyryl chloride (18.1g, 0.17 mole) was added slowly with stirring over 15 minutes. The ice bath was removed and the reaction stirred at room temperature for 3 hours. Water (100ml) was added to the reaction mixture and the organic fraction recovered from the mixture. The organic phase was washed with dilute hydrochloric acid (75ml, 2 molar), saturated aqueous sodium chloride (75ml) and then dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure. The residue was distilled under reduced pressure to yield the butyrate ester (20.g, 64% yield; 60-73°C/666,610 Pa (5mm Hg)). The product contained approximately 5% of the trans isomer.

[0018] NMR (CDCl₃): 0.95 (3H, m), 1.15-2.05 (9H, m), 2.30 (2H, m), 3.45 (2H, m), 4.0 (1H, m), 4.85 (1H, m).

EXAMPLE 2

Identification of Enzymes Hydrolysing Cis-2-Methyltetrahydro-(4H)-Pyran-4-ol Esters Enantioselectively

[0019] The enzymic hydrolysis of esters was carried out in a Mettler DL25 autotitrator to maintain the pH at the desired level. The extent of hydrolysis was conveniently calculated from the consumption of the titrant, sodium hydroxide.

[0020] The butyric ester (0.29g) was suspended as droplets in a buffer (30ml) of pH 7.5 comprising tris (hydroxymethyl) amino methane (10mM), sodium chloride (60mM) and calcium chloride (20mM). To this was added enzyme (100mg of solid or 2ml when a liquid). The temperature was held at 30°C and the reaction mixture stirred whilst pH was maintained by the automatic addition of aqueous sodium hydroxide (0.25 molar). A decrease in titration rate as hydrolysis approached 50% was used as an indication of enantioselectivity, promising reactions were extracted and analysed as follows. When the quantity of sodium hydroxide added was equivalent to the hydrolysis of 50% of the ester the reaction mixture was extracted with an equal volume of diethyl ether. Where immobilised enzyme was used this was removed by filtration prior to extraction with diethyl ether. The residual ester was recovered in the ether layer whilst the enzyme and the majority of the pyranol were present in the aqueous layer. The ether layer was washed with an equal volume of water to remove traces of pyranol from the organic layer. The diethyl ether fraction was dried over anhydrous sodium sulphate, the ether layer recovered by filtration and the butyric ester isolated from it by removal of the ether by distillation at reduced pressure.

[0021] The enantiomers of the butyric ester were measured by HPLC using a Chiralcel OB column, 250mm x 4.6mm (Daicel Chemical Industries Ltd) eluted with hexane : 2-propanol (99:1) at a rate of 1ml/minute. The ester was detected by UV absorption at 215nm. Under these conditions the (2S, 4S) butyric ester eluted at 5.7 minutes whilst the (2R, 4R) butyric ester eluted at 7.2 minutes. The results of the enzyme screen are shown in Table 1.

TABLE 1

Enzyme	Source	Hydrolysis	Ratio of Butyric Ester Enantiomers (S) : (R)
Chromobacterium viscosum	B	Yes	nd
Pseudomonas fluorescens	B	Yes	nd
Mucor miehei	B	No	nd
Geotrichum candidum	B	No	nd
Candida cylindracea	B	Yes	nd
Porcine pancreatic lipase	B	No	nd
Porcine liver esterase	S	Yes	nd
Lipase P	A	Yes	80 : 20
Lipase SAM II	A	Yes	80 : 20
Lipolase TM	N	Yes	> 95 : 5
Novozym 435 TM	N	Yes	> 95 : 5
nd not determined.			
B Biocatalysts Ltd, Main Avenue, Treforest Industrial Estate, Pontypridd CF37 5UT, United Kingdom.			
S Sigma Chemical, Fancy Road, Poole, Dorset BH17 7BR, United Kingdom.			

TABLE 1 (continued)

Enzyme	Source	Hydrolysis	Ratio of Butyric Ester Enantiomers (S) : (R)
A Amano Pharmaceutical Co Ltd, Eschersheimer Landstrasse 49, D-6000, Frankfurt am Main 1, Germany.			
N Novo Nordisk A/S, Novo allé, 2880 Bagsvaerd, Denmark.			

EXAMPLE 3**Preparative Scale Resolution of 2-Methyltetrahydro-(4H)-Pyran-4-ol Butyrate Ester using Lipase from Candida Antarctica (MOVOZYM 435™) and conversion to (S)-2-Methyltetrahydro-(4H)-Pyran-4-one**

[0022] To a 10 litre stirred glass reaction vessel was added water (4 litres) and tris (hydroxymethyl) amino methane free base (4.84g, 40 millimoles) to give a solution of pH 9.5. To this was added 2-methyltetrahydro-(4H)-pyran-4-ol butyrate ester (2.933Kg, 15.77 moles) resulting in a decrease in pH to 5.0. The pH of the stirred biphasic mixture was adjusted to pH 8.0 with sodium hydroxide (5 molar). Enzyme (30g of Novozym 435™ beads) was slurried in 100ml of water and added to the reactor to start the reaction. The pH was controlled at pH 7.8-8.0 by the automatic addition of sodium hydroxide solution (5 molar), the temperature was controlled at 28-32°C.

[0023] After 25 hours the reaction mixture was filtered through a Whatman GF/B glass fibre filter to remove the enzyme beads. The filtrate was allowed to settle and the upper organic layer recovered. Pentane (500ml) was added to the organic fraction which was then washed twice with deionised water (1 litre) to remove traces of pyranol from the organic fraction. The separated organic fraction was dried over anhydrous sodium sulphate and filtered. The filtrate was then distilled at reduced pressure to remove pentane yielding resolved (4S, 6S)-2-methyltetrahydro-(4H)-pyran-4-ol butyrate ester as a pale yellow oil. Ester recovered = 1.359Kg (46% yield, 96% chemical strength).

[0024] A sample of the resolved 2-methyltetrahydro-(4H)-pyran-4-ol butyrate ester was hydrolysed to the corresponding alcohol as follows. Butyrate ester (627.8g, 96% chemical strength) was added to a solution of sodium hydroxide (5 molar, 1200ml) and the mixture warmed to 70°C. After 1.5 hours the mixture was cooled to room temperature and saturated aqueous sodium chloride (600ml) was added. The mixture was extracted with diethyl ether (600ml x 11). The organic fractions were combined and dried over anhydrous magnesium sulphate, decolourised with charcoal and the solvent removed under reduced pressure to yield 2-methyltetrahydro-(4H)-pyran-4-ol (353.1g, 94% yield).

[0025] NMR (CDCl₃): 1.21 (3H, d), 1.5 (2H, m), 1.9 (2H, m), 3.4 (2H, m), 3.78 (1H, m), 4.0 (1H, m).

[0026] A sample of the 2-methyltetrahydro-(4H)-pyran-4-ol was oxidised to 2-methyltetrahydro-(4H)-pyran-4-one under the following conditions. 2-methyltetrahydro-(4H)-pyran-4-ol (119g) was added to acetone (2700ml) and cooled to 8°C on an ice bath. Chromic acid solution (234ml, 8N-prepared by adding 266.7g of chromium (VI) oxide to a mixture of 230ml of concentrated sulphuric acid and 400ml of water and made up to 1 litre with water) was added dropwise over 1 hour with rapid stirring. After a further 2 hours isopropanol (5ml) was added gradually until the colour of the solution turned green. The acetone solution was decanted and filtered. The residue was washed with acetone. The combined filtrate and washings were distilled under reduced pressure to remove acetone, the aqueous residue was then extracted with diethyl ether (500ml followed by 3 x 125ml). The combined extracts were dried over magnesium sulphate and the diethyl ether removed under reduced pressure. The residue was distilled under reduced pressure to yield the pyranone (92.4g, 79%, 60°C/80mm Hg). NMR (CDCl₃): 1.31 (3H, d), 2.2-2.64 (4H, m), 3.69 (2H, m), 4.28 (1H, m).

[0027] The enantiomeric purity of 2-methyltetrahydro-(4H)-pyran-4-one was determined by chiral stationary phase HPLC using the conditions described in Example 2. The (S)-enantiomer eluted at 15.6 minutes whilst the (R)-enantiomer eluted at 18.1 minutes. The reaction product consisted of 98% (S)-enantiomer, 2% (R)-enantiomer.

EXAMPLE 4**Resolution of Racemic Cis-2-Methyltetrahydro-(4H)-Pyran-4-ol by Enantioselective Transesterification Catalysed by NOVOZYM 435™ in the presence of Vinyl Butyrate**

[0028] To 20g of racemic cis-2-methyltetrahydro-(4H)-pyran-4-ol (0.172 mole) was added vinyl butyrate (14g, 0.123 mole) and Novozym 435™ immobilised enzyme preparation (0.2g). The reaction mixture was stirred at 28°C. The reaction was monitored for formation of butyrate ester and disappearance of pyranol by gas chromatography. Analysis was carried out using a Perkin-Elmer 8500 gas chromatograph fitted with a 30 metre x 0.32mm DB5 column (J & W Scientific). Helium (8psi) was the carrier gas and detection was by flame ionisation. The temperature programme consisted of an initial 1 minute at 100°C followed by an increase to 170°C at a rate of 20°C/minute, the temperature

was then maintained at 170°C for 10 minutes. The retention time of cis-2-methyltetrahydro-(4H)-pyran-4-ol was 6.1 minutes whilst that for the corresponding butyrate ester was 12.1 minutes. The rate of reaction decreased as it approached 50% esterification and the reaction stopped after 12 hours at 52.5% esterification.

[0029] The solution was filtered to remove the enzyme beads and then the filtrate was extracted twice with an equal volume of water to remove unreacted cis-2-methyltetrahydro-(4H)-pyran-4-ol. The combined aqueous extracts were then back-extracted twice with an equal volume of pentane to remove any trace of butyrate ester from the aqueous phase. The aqueous solution containing the cis-2-methyltetrahydro-(4H)-pyran-4-ol was then saturated with sodium chloride and extracted twice with an equal volume of ethyl acetate. The ethyl acetate extract was dried over anhydrous sodium sulphate and the solvent removed by distillation under reduced pressure to yield resolved cis-2-methyltetrahydro-(4H)-pyran-4-ol (8.86g).

[0030] The enantiomeric purity of the resolved cis-2-methyltetrahydro-(4H)-pyran-4-ol was determined by chiral stationary phase HPLC of the benzoyl ester. The benzoyl ester was synthesised as follows; To a 50ml stoppered tube was added cis-2-methyltetrahydro-(4H)-pyran-4-ol (0.2g, 1.724m mole), benzoic anhydride (0.39g, 1.725m mole), pyridine (5ml) and dimethylaminopyridine (5mg). The mixture was incubated at 60°C for 6 hours. The reaction mixture was cooled to room temperature, diluted to 50ml with diethylether and washed successively with 2 x 50ml hydrochloric acid (20 millimolar), sodium hydroxide (100 millimolar), distilled water and saturated aqueous sodium chloride. The organic layer was recovered, dried over anhydrous sodium sulphate and filtered. The filtrate was collected and the diethyl ether removed by distillation under reduced pressure to yield the benzoyl ester of cis-2-methyltetrahydro-(4H)-pyran-4-ol as a pale yellow oil.

[0031] The enantiomeric purity was determined using a Chiralcel OB column (Daicel Chemical Industries Ltd), 250mm x 4.6mm, eluted with hexane : ethanol (99.5 : 0.5) at a rate of 0.75ml/minute. The compounds were detected by UV absorption at 225nm. The retention times for the (2R, 4R) and (2S, 4S) enantiomers of the benzoyl ester derivative of 2-methyltetrahydro-(4H)-pyran-4-ol were 17.1 minutes and 21.7 minutes respectively. Analysis of the resolved sample indicated the optical purity to be 98.5% (2S, 4S), 1.5% (2R, 4R).

EXAMPLE 5

Resolution of Racemic Cis-2-Methyltetrahydro-(4H)-Pyran-4-ol by Enantioselective Transesterification Catalysed by NOVOZYM 435™ In the presence of Vinyl Acetate

[0032] To 2g of racemic cis-2-methyltetrahydro-(4H)-pyran-4-ol (17.2 millimoles) was added 1.01g of vinyl acetate (12.9 millimoles) and 0.1g of immobilised enzyme preparation Novozym 435™. The reaction mixture was stirred at 28°C and the reaction monitored by gas chromatography as described in Example 4. The retention time of the acetyl ester of cis-2-methyltetrahydro-(4H)-pyran-4-ol was 8.2 minutes. The reaction was halted when 58% of the pyranol had been converted to the acetyl ester (4 hours). The reaction mixture was processed as described in Example 4 to yield 0.57g of resolved cis-2-methyltetrahydro-(4H)-pyran-4-ol. The benzoyl ester derivative was prepared as in Example 4 and analysed by chiral stationary phase HPLC also as described in Example 4. Analysis of the resolved sample indicated the optical purity to be 99% (2S, 4S), 1% (2R, 4R).

Claims

1. A process of producing an optically active cis 2- substituted tetrahydropyran-4-ol or ester thereof which comprises stereospecifically esterifying a cis 2- substituted tetrahydropyran-4-ol using a stereospecific esterase or stereospecifically hydrolysing an ester thereof with a stereospecific hydrolase.
2. A process of producing an optically active 2- substituted tetrahydropyran-4-one which comprises stereospecifically esterifying a cis-2-substituted tetrahydropyran-4-ol using a stereospecific esterase or stereospecifically hydrolysing an ester thereof with a stereospecific hydrolase, and oxidising the alcohol product to the corresponding ketone preferably after separating it from the ester and/or separating the ester and alcohol or ketone products, hydrolysing the ester to the corresponding alcohol and oxidising the resulting alcohol to the corresponding ketone.
3. A process of producing an optically active cis 2- substituted tetrahydropyran-4-ol or ester thereof which comprises producing a cis-racemic 2-substituted tetrahydropyran-4-ol by reacting but -3-ene- 1-ol with an aldehyde of formula XCHO in which X is the desired 2-substituent of the pyranol in the presence of an acid, esterifying the racemic mixture using a stereospecific esterase or esterifying the racemic mixture optionally non stereospecifically and hydrolysing it with a stereospecific hydrolase.

4. A process of producing an optically active 2- substituted tetrahydropyran-4-one which comprises producing a cis-racemic 2-substituted tetrahydropyran-4-ol by reacting but -3-ene- 1-ol with an aldehyde of formula XCHO in which X is the desired 2-substituent of the pyranol in the presence of an acid, esterifying the racemic mixture using a stereospecific esterase or esterifying the racemic mixture optionally non stereospecifically and hydrolysing it with a stereospecific hydrolase and oxidising the resulting alcohol or an alcohol derived from the resulting ester to the corresponding ketone by hydrolysis.
5. A process as claimed in Claim 1,3 or 4 in which the ester is separated from the alcohol.
6. A process as claimed in any of Claims 1 to 4 in which the alcohol is further reacted to a desired product in the presence of the ester.
7. A process as claimed in any of Claims 1 to 5 in which if the alcohol stereoisomer is required it is hydrolysed, optionally stereospecifically.
8. A process as claimed in any preceding claim which comprises a stereospecific esterification and a stereospecific hydrolysis.
9. A process as claimed in any preceding claim in which the 2-substituent is an alkyl or substituted alkyl group.
10. A process as claimed in any preceding claim in which the esterification is a transesterification with a vinyl ester.
11. A process as claimed in any preceding claim in which the cis 2-substituted tetrahydropyranol is cis 2-methyl tetrahydropyranol or cis 2-ethyl tetrahydropyranol.
12. A process as claimed in any preceding claim in which the esterification is carried out in the presence of a quantity of water not substantially greater than the minimum necessary to secure the optimum effectiveness of the enzyme.
13. A process as claimed in any preceding claim in which the enzyme is derived from *Humicola lanuginosa*, *Pseudomonas* or *Candida antarctica*.
14. A process as claimed in any preceding claim in which an alcohol is produced and converted to a ketone by reacting it with a strong oxidising agent in the presence of a strong acid and an inert organic solvent.

Patentansprüche

1. Verfahren zum Herstellen eines optisch aktiven cis-2-substituierten Tetrahydropyran-4-ols oder Esters davon, umfassend das stereospezifische Verestern eines cis-2-substituierten Tetrahydropyran-4-ols unter Verwenden einer stereospezifischen Esterase oder stereospezifisches Hydrolysieren eines Esters davon mit einer stereospezifischen Hydrolase.
2. Verfahren zum Herstellen eines optisch aktiven 2-substituierten Tetrahydropyran-4-ons, umfassend das stereospezifische Verestern eines cis-2-substituierten Tetrahydropyran-4-ols unter Verwenden einer stereospezifischen Esterase oder stereospezifisches Hydrolysieren eines Esters davon mit einer stereospezifischen Hydrolase, und Oxidieren des Alkohol-Produkts zu dem entsprechenden Keton, bevorzugt nach Trennen von dem Ester und/oder Trennen der Ester- und Alkohol- oder Keton-Produkte, Hydrolysieren des Esters zu dem entsprechenden Alkohol und Oxidieren des resultierenden Alkohols zu dem entsprechenden Keton.
3. Verfahren zum Herstellen eines optisch aktiven cis-2-substituierten Tetrahydropyran-4-ols oder Ester davon, umfassend das Herstellen eines cis-racemischen 2-substituierten Tetrahydropyran-4-ols durch Reagieren von But-3-en-1-ol mit einem Aldehyd der Formel XCHO, in dem X der gewünschte 2-Substituent des Pyranols ist, in Gegenwart einer Säure, Verestern der racemischen Mischung unter Verwenden einer stereospezifischen Esterase oder optional nicht-stereospezifisches Verestern der racemischen Mischung und Hydrolysieren mit einer stereospezifischen Hydrolase.
4. Verfahren zum Herstellen eines optisch aktiven 2-substituierten Tetrahydropyran-4-ons, umfassend das Herstellen eines cis-racemischen 2-substituierten Tetrahydropyran-4-ols durch Reagieren von But-3-en-1-ol mit einem Alde-

hyd der Formel $XCHO$, in der X der gewünschte 2-Substituent des Pyranols ist, in Gegenwart einer Säure, Verestern der racemischen Mischung unter Verwenden einer stereospezifischen Esterase oder optional nicht-stereospezifisches Verestern der racemischen Mischung und Hydrolysieren mit einer stereospezifischen Hydrolase, und Oxidieren des resultierenden Alkohols oder eines von dem resultierenden Ester mittels Hydrolyse abgeleiteten Alkohols zu dem entsprechenden Keton.

5. Verfahren gemäß Anspruch 1, 3 oder 4, in dem der Ester von dem Alkohol getrennt wird.
6. Verfahren gemäß einem der Ansprüche 1 bis 4, in dem der Alkohol weiter zu einem gewünschten Produkt in Gegenwart des Esters reagiert wird.
7. Verfahren gemäß einem der Ansprüche 1 bis 5, in dem, falls das Alkohol-Stereoisomer benötigt wird, es, optional stereospezifisch, hydrolysiert wird.
8. Verfahren gemäß einem der vorhergehenden Ansprüche, das eine stereospezifische Veresterung und eine stereospezifische Hydrolyse umfaßt.
9. Verfahren gemäß einem der vorhergehenden Ansprüche, in dem der 2-Substituent eine Alkyl- oder substituierte Alkyl-Gruppe ist.
10. Verfahren gemäß einem der vorhergehenden Ansprüche, in dem die Veresterung eine Umesterung mit einem Vinylester ist.
11. Verfahren gemäß einem der vorhergehenden Ansprüche, in dem das cis-2-substituierte Tetrahydropyranol cis-2-Methyltetrahydropyranol oder cis-2-Ethyltetrahydropyranol ist.
12. Verfahren gemäß einem der vorhergehenden Ansprüche, in dem die Veresterung in Gegenwart einer Menge an Wasser, die nicht wesentlich größer als das zum Sicherstellen der optimalen Aktivität des Enzyms notwendige Minimum ist, durchgeführt wird.
13. Verfahren gemäß einem der vorhergehenden Ansprüche, in dem das Enzym abgeleitet ist von *Humicola lanuginosa*, *Pseudomonas* oder *Candida antarctica*.
14. Verfahren gemäß einem der vorhergehenden Ansprüche, in dem ein Alkohol hergestellt und durch Reagieren mit einem starken Oxidationsmittel in Gegenwart einer starken Säure und einem inerten organischen Lösungsmittel zu einem Keton umgewandelt wird.

Revendications

1. Procédé de production d'un cis-2-tétrahydropyran-4-ol 2-substitué optiquement actif ou d'un ester de celui-ci qui comprend l'estérification stéréospécifique d'un cis-tétrahydropyran-4-ol 2-substitué au moyen d'une estérase stéréospécifique ou l'hydrolyse stéréospécifique d'un ester de celui-ci avec une hydrolase stéréospécifique.
2. Procédé de production d'une tétrahydropyran-4-one 2-substituée optiquement active qui comprend l'estérification stéréospécifique d'un cis-tétrahydropyran-4-ol 2-substitué au moyen d'une estérase stéréospécifique ou l'hydrolyse stéréospécifique d'un ester de celui-ci avec une hydrolase stéréospécifique, et l'oxydation du produit alcool en la cétone correspondante de préférence après sa séparation de l'ester et/ou après la séparation de l'ester et des produits alcool ou cétone, l'hydrolyse de l'ester en l'alcool correspondant et l'oxydation de l'alcool résultant en la cétone correspondante.
3. Procédé de production d'un cis-tétrahydropyran-4-ol 2-substitué optiquement actif ou d'un ester de celui-ci qui comprend la production d'un cis-tétrahydropyran-4-ol 2-substitué racémique par réaction du but-3-én-1-ol avec un aldéhyde de formule $XCHO$ où X est le 2-substituant voulu du pyranol en présence d'un acide, l'estérification du mélange racémique au moyen d'une estérase stéréospécifique ou l'estérification du mélange racémique éventuellement de manière non stéréospécifique et son hydrolyse avec une hydrolase stéréospécifique.
4. Procédé de production d'une tétrahydropyran-4-one 2-substituée optiquement active qui comprend la production

- d'un cis-tétrahydropyran-4-ol 2-substitué racémique par réaction du but-3-én-1-ol avec un aldéhyde de formule XCHO où X est le 2-substituant voulu du pyranol en présence d'un acide, l'estérification du mélange racémique au moyen d'une estérase stéréospécifique ou l'estérification du mélange racémique éventuellement de manière non stéréospécifique et son hydrolyse avec une hydrolase stéréospécifique et l'oxydation de l'alcool résultant ou d'un alcool issu de l'ester résultant en la cétone correspondante par hydrolyse.
- 5 5. Procédé selon la revendication 1, 3 ou 4, où l'ester est séparé de l'alcool.
 - 10 6. Procédé selon l'une quelconque des revendications 1 à 4, où l'alcool est mis à réagir encore en un produit voulu en présence de l'ester.
 7. Procédé selon l'une quelconque des revendications 1 à 5, où, si le stéréoisomère de l'alcool est nécessaire, il est hydrolysé, éventuellement de manière stéréospécifique.
 - 15 8. Procédé selon l'une quelconque des revendications précédentes, qui comprend une estérification stéréospécifique et une hydrolyse stéréospécifique.
 9. Procédé selon l'une quelconque des revendications précédentes, où le 2-substituant est un groupe alkyle ou alkyle substitué.
 - 20 10. Procédé selon l'une quelconque des revendications précédentes, où l'estérification est une transestérification avec un ester de vinyle.
 - 25 11. Procédé selon l'une quelconque des revendications précédentes, où le cis-tétrahydropyranol 2-substitué est le cis-2-méthyltétrahydropyranol ou le cis-2-éthyltétrahydropyranol.
 12. Procédé selon l'une quelconque des revendications précédentes, où l'estérification est conduite en présence d'une quantité d'eau qui n'est pas sensiblement supérieure au minimum nécessaire pour garantir l'efficacité optimale de l'enzyme.
 - 30 13. Procédé selon l'une quelconque des revendications précédentes, où l'enzyme est issue de *Humicola lanuginosa*, *Pseudomonas* ou *Candida antarctica*.
 - 35 14. Procédé selon l'une quelconque des revendications précédentes, où un alcool est produit et converti en une cétone par réaction avec un agent oxydant fort en présence d'un acide fort et d'un solvant organique inerte.

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